CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FLUROXYPYR

Chemical Code # 5768, **Tolerance #** 52860
SB 950 # NA

December 18, 2003

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect indicated
Chronic toxicity, dog:	No data gap, no adverse effect indicated
Oncogenicity, rat:	No data gap, no adverse effect indicated
Oncogenicity, mouse:	No data gap, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect indicated
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, no adverse effect indicated
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 208091 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T031218
Revised by T. Moore, 12/18/03

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 0025, 0051; 201861, 205044**; "Fluroxypyr: Two Year Dietary Chronic Toxicity/Oncogenicity Study in Fischer 344 Rats - Final Report"; (J.F. Quast and R.J. McGuirk; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. K-129976-008; 6/15/95); Fifty Fischer 344 rats/sex/group were treated in the diet with 0, 100, 500 or 1000 mg/kg/day of Fluroxypyr technical (lot no. AGR 295035, purity: 99.0%) for 2 years. Additional 10 animals/sex/group for each study group were treated with the test material for 1 year. Individual males in the 1000 mg/kg group exhibited erratic weight gains and moribundity due to excessive toxicity of the treatment during the first 3 months of the study. These effects were sufficiently severe as to warrant the removal of all of the males in this group from the study on day 118. For this group, after 13 weeks of treatment, the blood urea nitrogen was increased over that of the control, the specific gravity of the urine was lower than that of the controls ($p<0.05$). Histological examination of their kidneys revealed pelvic epithelial hyperplasia (19/60), necrosis of the papillae (22/60), and moderate to very severe chronic regenerative nephrosis (51/60). The mean body weights for the 1000 mg/kg males were lower than those of the control from the initiation of the study until their removal. Likewise, the mean body weights of the 1000 mg/kg females were lower than those of the control throughout the study ($p<0.05$). Mean food consumption was not affected by the treatment. Although the mean hematocrit values for the 1000 mg/kg females at various times during the study were lower than those of the control animals ($p<0.05$), no physiologically significant effect upon the hematological parameters was noted. Blood urea nitrogen and the BUN/creatinine ratios were increased for the 500 mg/kg males and the 1000 mg/kg females at the termination of the study. The specific gravity of the urine for the 1000 mg/kg females was lower than that of the control over the course of the study ($p<0.05$). In the necropsy examination, the mean relative kidney weights of the 500 mg/kg males and the 100, 500 and 1000 mg/kg females at 12 and 24 months were greater than those of the control ($p<0.05$). The mean relative liver weights for the 500 mg/kg males and for the 500 and 1000 mg/kg females were greater than those of the controls at 24 months ($p<0.05$). At 24 months, there were increased numbers of animals in the 500 and 1000 mg/kg groups with kidneys having a roughened surface ((M): 0: 8/50 vs. 500: 16/50; (F): 0: 0/50 vs. 500: 7/50, 1000: 26/50). In the histology examination, very slight and slight bilateral hypertrophy of the zona glomerulosa in the adrenal glands was noted for the 1000 mg/kg females (0: 0/50 vs. 1000: 31/50). In the kidneys, an increased incidence of moderate to very severe chronic progressive glomerulonephropathy (unilateral and bilateral) for the 1000 mg/kg females was evident (0: 2/50 vs. 1000: 30/50). An increased incidence of multifocal erosion and/or ulceration in the glandular mucosa of the stomach for the 1000 mg/kg females was noted (0: 2/50 vs. 1000: 8/50, $p<0.05$). **Possible adverse effect:** renal lesions. **Chronic NOEL:** (M) 100 mg/kg/day (based upon treatment-related effects on kidney function of the 500 mg/kg males), (F) 500 mg/kg/day (based upon treatment-related effects on kidney function of the 1000 mg/kg females); **No oncogenicity evident.** Study previously unacceptable, possibly upgradeable with the submission of the actual concentrations of the active ingredient in the dietary preparations; information submitted in vol.52860-0051, rec. no. 205044 was sufficient to upgrade the study. (Moore, 2/20/03, upgraded, Moore, 8/11/03).

CHRONIC TOXICITY, RAT

See Combined, Rat above

CHRONIC TOXICITY, DOG

0059; 208091; "12-Month Toxicity Study in Beagle Dogs by Dietary Administration of Dowco 433"; (H.J. Kinkel; Battelle Institute, Frankfurt am Main, Germany; Project ID. V-65 541; 12/12/84); Four beagle dogs/sex/group received 0, 20, 50 or 150 mg/kg/day of Dowco 433 (lot no. 433 t-0283-10, purity: 98%) in the diet for 52 weeks. One male dog in the 20 mg/kg group died during week 12 due to a non-treatment related condition. There were no treatment-related effects noted on the mean body weights, body weight gain, food consumption, hematology, clinical chemistry,

and urinalysis. The necropsy and histopathological examinations did not reveal any treatment-related lesions or target organs. **No advers effect indicated. NOEL:** (M/F) 150 mg/kg/day (based upon the lack of any treatment-related effects at the highest dose tested). **Study unacceptable**, not upgradeable (The selected doses were not adequate to establish a dose-related response to the test material as required in the guidelines). (Moore, 12/15/03)

ONCOGENICITY, RAT

See Combined, Rat above

ONCOGENICITY, MOUSE

** 0019, 0051; 201855, 205044; “Fluroxypyr: 18-Month Dietary Oncogenicity Study in CD-1 Mice”; (P.F. Cosse, J.W. Crissman, D.A. Markham and R.A. Corley; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID: K-129976-004; 7/20/93); Sixty CD-1 mice/sex/group received 0, 100, 300 or 1000 mg/kg/day of Fluroxypyr Technical (lot no. AGR# 279095, purity: 98.9%) in the diet for 18 months. There were no treatment-related effects upon survivability. Treatment resulted in a significantly lower mean body weights in the high dose males ($p<0.05$). There was no treatment-related effect upon the hematology parameters. The females in the 1000 mg/kg group demonstrated increased incidences of kidney lesions (necrosis of papillae: 0 (3/60), 1000 (12/60); chronic nephrosis (severe or very severe): 0 (2/60), 1000 (7/60)) ($p<0.05$, positive trend test (alpha=0.02). **No adverse effect indicated. Chronic Toxcity (M):** 300 mg/kg/day (based upon reduced body weight of the 1000 mg/kg males); **(F):** 300 mg/kg/day (based upon renal lesions noted for the 1000 mg/kg females); **No oncogenicity evident.** Study previously unacceptable; possibly upgradeable to acceptable with the submission of the actual concentrations of the test material in the dietary preparations; information submitted in vol.52860-0051, rec. no. 205044 was sufficient to upgrade the study. (Moore, 1/31/03, upgraded, Moore, 8/11/03)

REPRODUCTION, RAT

001 178370; " Fluroxypyr: Two Generation Dietary Reproductive Toxicity Study in Sprague-Dawley Rats " (U. Vedula, *et al*; Dow Chemical Company, Health & Environmental Research Laboratories, Midland, MI; Lab Study No. K-129976-012; 6/19/96 (revised 11/10/97)); Fluroxypyr (Lot No. AGR 295035; purity = 99%) was administered in the diet to groups of 30 animals/sex/dose level at 0 (diet), 100, 500 and 750 (M)/1000 (F) mg/kg/day continuously for three generations (two F2 generations were produced due a technical error in which the incorrect chemical was fed to F1 adults for up to 5 days); reduced food consumption and weight gain, and renal toxicity (increased kidney weight, gross and microscopic kidney lesions) and mortality were observed at the high-dose, with increased kidney weight and some kidney lesions also evident in mid-dose males (the parental NOEL was 500 mg/kg/day (F) and 100 mg/kg/day (M)); no effects on reproductive parameters were noted in any generation (reproductive NOEL = 1000 mg/kg/day (F), 750 mg/kg/day (M)); high-dose litters showed slightly increased mortality, and reduced pup weight and growth (developmental NOEL = 500 mg/kg/day); **Acceptable. (Duncan, 4/17/01)

TERATOLOGY, RAT

** 0022; 201858; “A Developmental Toxicity Study in Rats with Fluroxypyr Methylheptyl Ester”; (R.E. Schroeder; Pharmaco LSR, Inc., Toxicology Services North America, East Millstone, NJ; Study ID. 93-4052; 5/3/94); Twenty eight mated female CD (SD) BR (Sprague-Dawley derived) rats/group were dosed orally by gavage with 0 (corn oil), 100, 300 or 600 mg/kg/day of Fluroxypyr methylheptyl ester technical (lot no. EX TV 275-31 (AGR 283750), purity: 95.8%) from day 6 through day 15 of gestation. Eight of the 600 mg/kg group females died between days 10 and 17 of gestation. Mean body weight gain of the 600 mg/kg group females was lower than that of the controls during the dosing period ($p<0.05$ for days 12 to 16). For the females that died, lethargy, hypothermia, labored breathing, pale appearance and irregular gait were noted. There were no treatment-related effects upon the development of the fetuses. **No adverse effect evident. Maternal NOEL:** 300 mg/kg/day (based upon the reduced body weight gain and incidence of death for the dams in the 600 mg/kg treatment group); **Developmental NOEL:** 600 mg/kg/day (no treatment-related effects at the highest dose tested); **Study acceptable.** (Moore, 2/4/03)

0020; 201856; "A Range-Finding Study to Evaluate the Developmental Toxicity of Fluroxypyr Methylheptyl Ester in the Rat"; (R.E. Schroeder; Pharmaco LSR, Inc., Toxicology Services North America, East Millstone, NJ; Study ID 93-4051; 5/3/94); Ten CD (SD) BR (Sprague-Dawley derived) mated female rats/group were dosed orally by gavage with 0 (corn oil), 100, 500, 750, or 1000 mg/kg/day of Fluroxypyr Methylheptyl Ester (lot no. EXTV 275-31(AGR 283750), purity: 95.8%) from day 6 through day 15 of gestation. Four animals in the 750 mg/kg group and 7 animals in the 1000 mg/kg group died prior to the termination of the study on day 16 of gestation. The remaining 3 females in the 1000 mg/kg group were euthanized on day 11. The mean absolute and relative kidney weights for the 750 mg/kg females were greater than those of the control ($p<0.05$ and $p<0.01$). There were no apparent treatment-related effects upon the fetuses. **No adverse effects indicated. NOEL not determined. Study supplemental** (non-guideline study). (Moore, 2/3/03)

TERATOLOGY, RABBIT

** 0024; 201860; "Fluroxypyr Methylheptyl Ester: Oral Gavage Teratology Study in New Zealand White Rabbits"; (A.B. Liberacki, W.J. Breslin, and J.F. Quast; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. K-137992-013; 5/2/96); Twenty mated New Zealand White female rabbits/group were dosed orally by gavage with 0 (0.5% Methocel A4M), 100, 500 or 1000 mg/kg/day of Fluroxypyr Methylheptyl Ester Technical (lot no. AGR283750, purity: 95.8%) (equivalent to 0, 69, 346 and 693 mg/kg/day of fluroxypyr acid) from day 7 through day 19 of gestation. One female in the 1000 mg/kg group died as a result of a dosing accident. Three does in the 1000 mg/kg group and one in the 500 mg/kg group aborted. Two of the 3 animals in the former group exhibited decreased food consumption and body weight loss prior to aborting on day 25. Otherwise, there were no apparent treatment-related effects upon body weight gain or food consumption. There was no treatment-related effect upon the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 500 mg/kg/day (based upon the incidence of abortions for the 1000 mg/kg treatment group), **Developmental NOEL:** 1000 mg/kg/day (based upon the lack of treatment-related effects for the 1000 mg/kg treatment group); **Study acceptable.** (Moore, 2/7/03)

0023; 201859; "Fluroxypyr Methylheptyl Ester: Oral Gavage Teratology Probe Study in New Zealand White Rabbits"; (A.B. Liberacki, W.J. Breslin and J.F. Quast; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. K-137992-012; 5/2/96); Seven mated New Zealand White females/group were dosed orally by gavage with 0 (0.5% Methocel A4M), 300, 500, 750 or 1000 mg/kg/day of Fluroxypyr Methylheptyl Ester Technical (lot no. AGR283750, purity: 95.8%) from day 7 through day 19 of gestation (equivalent to 0, 208, 347, 520 and 693 mg/kg/day of fluroxypyr acid). In the 750 mg/kg treatment group, one female died on day 17 and two more in moribund condition were euthanized on day 18. All three animals apparently died as a result of dosing accidents. There were no treatment-related clinical signs or treatment-related effects upon mean body weight gain. The mean absolute and relative kidney weights of the 1000 mg/kg treatment group were greater than those of the controls. There was no apparent treatment-related effect upon the number of fetuses per litter. **No adverse effect evident. NOEL not determined. Study supplemental** (non-guideline study). (Moore, 2/5/03)

GENE MUTATION

** 0027; 201863; "Evaluation of Fluroxypyr Methylheptyl Ester in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay"; (V.A. Linscombe and J.R. Ormand; Health and Environmental Sciences, The Toxicology Research Laboratory, The Dow Chemical Company, Midland, MI; Study ID. K-137992-009; 1/23/96); Chinese Hamster Ovary (CHO-K_1-BH_4) cells were exposed to Fluroxypyr Methylheptyl Ester Technical (AGR283750; purity: 95.8%) at concentrations ranging from 0 to 50.0 ug/ml (non-activation) and from 0 to 1200 ug/ml (activation) for 4 hours at 37^o C. Two trials were performed with duplicate cultures for each treatment level. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the mutation

frequency of the 6-thioguanine-resistant colonies. The positive controls were functional. **No adverse effect indicated. Study acceptable.** (Moore, 2/25/03)

** 0027; 201865; "Mutagenicity Test with Fluroxypyr Methylheptyl Ester in the *Salmonella-Escherichia Coli/*Mammalian-Microsome Reverse Mutation Assay Preincubation Method with Confirmatory Assay"; (T.E. Lawlor; Corning Hazleton Inc. (CHV), Vienna, VA; Study No. 16848-0-422R; 12/28/95); *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WP2uvrA were treated with Fluroxypyr Methylheptyl Ester Technical (lot no. AGR283750, purity: 95.8%) at concentrations ranging from 0 to 5000 ug/plate with a preincubation of 20 minutes and an incubation with plate incorporation for 48 hours at 37^{O} C under conditions of activation and non-activation. Two trials were performed with triplicate samples for each treatment level. An Arochlor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 2/27/03)

CHROMOSOME EFFECTS

** 0026; 201862; "Evaluation of Fluroxypyr Methylheptyl Ester in an *In Vitro* Chromosomal Aberration Assay Utilizing Rat Lymphocytes"; (V.A. Linscombe and K.E. Eagle; Health and Environmental Sciences, The Toxicology Research Laboratory, The Dow Chemical Company, Midland, MI; Study ID. K-137992-010; 1/16/96); Primary lymphocyte cultures, procured from the whole blood of male Sprague-Dawley rats (stimulated with PHA for 48 hours), were treated with 0 to 1250 ug/ml of Fluroxypyr Methylheptyl Ester Technical (AGR283750, purity: 95.8%) for 24 hours (non-activation) or 4 hours, followed by 20 hours of incubation (activation) in assay 1. In assay 2, the cells were treated with 0 to 270 ug/ml of the test material for 24 hours (non-activation) and then harvested or incubated for an additional 24 hours or 4 hours, followed by incubations of either 20 or 44 hours prior to being harvested (activation). An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. The positive controls were functional. A treatment-related increase in chromosomal aberration was not evident under either conditions of non-activation or activation. **No adverse effect indicated. Study acceptable.** (Moore, 2/24/03)

DNA DAMAGE

** 0027; 201864; "Evaluation of Fluroxypyr Methylheptyl Ester in the Mouse Bone Marrow Micronucleus Test"; (S.J. Lick, B.B. Gollapudi, and J.R. Ormand; Health and Environmental Sciences, The Toxicology Research Laboratory, The Dow Chemical Company, Midland, MI; Study ID. K-137992-011; 1/15/96); Fifteen CD-1 mice/sex/group were dosed orally by gavage with 0 (corn oil), 225, 450 or 900 mg/kg of Fluroxypyr Methylheptyl Ester Technical (AGR283750; purity: 95.8%). Five animals/sex/group/time point were euthanized at 24, 48 and 72 hours post-dose. In addition, 5 animals/sex/group were dosed with 120 mg/kg of cyclophosphamide (positive control) and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and the percentage of polychromatic erythrocytes (PCE) which were micronucleated was determined. The percentage of PCE's in the erythrocyte population was calculated as well. There was no treatment-related increase in the percentage of micronucleated PCE. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 2/26/03)

NEUROTOXICITY

Not required at this time.

SUBCHRONIC STUDIES

(90-day feeding study)

52860-0018; 201854; "13-Week Dietary Toxicity Study and 4-Week Recovery Study in Fischer 344 Rats"; (M. Grandjean, J.R. Szabo, and N.L. Davis; Health and Environmental Sciences-Texas, Lake Jackson Research Center, The Dow Chemical Company, Freeport, TX; Study ID: K-129976-007; 6/24/92); Ten Fischer 344 rats/sex/group received 0, 320, 700 or 1000 mg/kg/day of Fluroxypyr Technical (AGR-279095, purity: 98.9%) in the diet for 13 weeks. An additional 10 animals/sex/group were dosed with 0 or 1000 mg/kg/day of the test material for 13 weeks and then maintained for a 4 week recovery period. No deaths occurred during the study. The mean

body weight for the 1000 mg/kg males was lower than that of the controls over the course of the study ($p<0.05$). The red blood cell count, hemoglobin concentration and hematocrit of both sexes in the 1000 mg/kg group were lower than that of the controls ($p<0.05$). The red cell count and hemoglobin concentration were also lower for the 700 mg/kg males ($p<0.05$). No effect on the hematology was noted for the males in the 1000 mg/kg recovery group (females were not evaluated). Relative kidney weights for both the males and females in the 1000 mg/kg group were greater than those of the controls ($p<0.05$). This effect on the kidneys was noted for the males in the 1000 mg/kg recovery group with increased mean absolute and relative weights ($p<0.05$). The relative liver weights of the 1000 mg/kg group females were also increased over that of the controls after 13 weeks of treatment ($p<0.05$). No treatment-related lesions were noted in the histopathology examination. **No adverse effect indicated. Subchronic NOEL (M)** 320 mg/kg/day (based upon reduced red blood cell count and hemoglobin concentration noted for the 700 mg/kg treatment group), **(F)** 700 mg/kg/day (based upon treatment-related effects upon hematology and relative kidney and liver weights of the 1000 mg/kg treatment group); **Study acceptable.** (Moore, 1/29/03)

METABOLISM STUDIES

52860-0028; 201866; "Fluroxypyr Methylheptyl Ester (Fluroxypyr MHE) and Methylheptanol: Metabolism in Male Fischer 344 Rats"; (J.Y. Domoradzki and K.A. Brzak; The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI; Study ID. HET K-137992-014; 6/3/96); Eight male Fischer 344 rats/group were treated orally by gavage with either 17.7 mg/kg of 1-methylheptanol-1-^{14}C (B930-93, radiochemical purity: 97.5%, specific activity: 24.2 mCi/mmole) or 50.0 mg/kg of Fluroxypyr 1-methylheptyl-1-^{14}C-ester (B930-96, radiochemical purity: 99%, specific activity: 25.3 mCi/mmole). Five animals/group were included in a pharmacokinetic study in which plasma samples were drawn from an in-dwelling catheter at 10, 20 , 30, 45 minutes and 1, 1.5, 2, 3, 5, 7, 10, 12, 24, 48 hours post-dose. The 3 remaining animals/group were included in an excretion balance study in which urine, cage wash and CO_2 samples were collected at 12, 24, 36 and 48 hours post-dose and fecal samples were collected at 24 and 48 hours. The pharmacokinetic parameters and excretion profiles for both test materials are very similar. The study results indicate that the metabolic profile of the methylheptanol moiety of fluroxypyr methylheptyl ester is quite similar to that of methylheptanol itself. **Study supplemental** (non-guideline study). (Moore, 3/3/03)

52860-0057; 208089; "The Biokinetics and Metabolism of ^{14}C-DowCo 433 Methylheptyl Ester in Rats"; (R. Hawkins, D. Kirkpatrick, B. Conway, C.M. Finn, and B.R. Whitby; Department of Chemical Metabolism and Radiosynthesis, Huntingdon Research Centre, Huntingdon, Cambridgeshire, England; Project ID. DWC 314/80844; 1/5/81); Five substudies were performed in which CD rats were dosed orally by gavage with 50 mg/kg in single or multiple daily doses of ^{14}C-Dowco 433 MHE (lot no. 6-HD-0113-39a, specific activity: 61.8 uCi/mg, radiochemical purity: 99%) mixed with non-radiolabeled Dowco 433 MHE (lot no. EMJ 211178) with a final specific activity of 0.937 uCi/mg and a radiochemical purity of 98%. The dosing material was mixed in olive oil and administered at a volume of 2.5 ml/kg. The radiolabel was located on the pyridinyl ring. In Study A, (excretion study), 3 animals/sex were dosed for 7 days, followed by 5 days of sample collection. In Study B. (plasma analysis), one group of 3 animals/sex received a single dose, followed by 5 days of sample collection. A second group of 3 animals/sex were dosed daily for 7 days, followed by 5 days of sample collection. In Study C (tissue distribution), 5 animals/sex were dosed daily for 7 days, followed by serial sacrifices of 1 animal/sex/time at 1, 7, 24, 72 and 168 hours after the last dose. In Study D (whole body autoradiography), 6 males were dosed daily for 7 days**,** followed by serial sacrifices of 1 animal/sex/time at 1, 7, 24, 72 and 168 hours after the last dose. In Study E (biliary excretion), two animals/sex received a single dose, followed by 2 days of sample collection. In the excretion study, approximately 92% of the administered dose was ultimately excreted in the urine with no difference between the sexes. Between 90 and 96% of the first administered dose was excreted within 24 hours. In the bile duct cannulated rats, only 60 to 64% of the administered dose was recovered in the urine within the 48 hours post-dose with 26 to 29% of the dose recovered in the feces. Only 0.7% of the dose was recovered in the bile. The

authors reasoned that the absence of bile in the gastrointestinal tract resulted in reduced absorption of the test material and thereby reduced the excretion observed in the urine. Peak plasma concentration levels of radiolabeling were observed within the 1st hour post-dose after a single dose and within the first two hours post-dose after multiple doses. The radiolabel within the tissues was largely localized within the kidneys, gastrointestinal tract and blood with a progressive diminution of the concentrations in these sites over the 7 day sample collection period. The clarity of the autoradiographic pictures was too poor to make any more than a very general characterization of the distribution. More than 93% of the excreted radiolabel was identified as Dowco 433. Metabolic transformation of the test material was largely by ester hydrolysis. **Study supplemental** (protocols used in the study were non-guideline). (Moore, 12/17/03)

52860-0058; 208090; "Dowco 433 Pharmacokinetic Study in Male Wistar Rats"; (G.E. Veenstra and E.A. Herman; Health & Environmental Sciences, Toxicology Research Laboratory, Midland, MI; Project ID. HET K-1299F6-002; 6/1/83); Three fasted male Wistar rats/group were dosed orally by gavage with 20 or 200 mg/kg or intravenously through an implanted jugular cannula with 20 mg/kg of ^{14}C-Dowco 433 (ref. no. GHD-1030-44a, radiochemical purity: >99%, specific activity: 22.7 mCi/mmole). The radiolabel was sited at the 2 and 6 positions of the pyridinyl ring. The dosing preparation was prepared by diluting this radiolabeled material with unlabeled Dowco 433 (ref. no. 230-75-42/43, purity: 99.5%) such that each animal received 5 uCi/dose. The dose was administered in an aqueous NaOH vehicle (pH adjusted to 6.5). Samples of heparinized blood were collected at specified time intervals (up to 48 hours for the oral treatments and up to 24 hours post-dose for the iv treatment). Urine was collected at 6, 12, 24 and 48 (except for iv treatment) hours post-dose . Feces were recovered at 24 hour intervals after dosing. Urinary excretion was the major route of elimination, accounting for 88 to 94% of the administered radioactivity. Residual radioactivity in the tissues was quite minimal at 24 or 48 hours post-dose. The absorption half life was determined to be 1.3 hours. Plasma concentration-time demonstrated a biphasic profile with a fast elimination half life of 4.2 minutes and a terminal elimination half life of 6.4 hours. The AUC (ug hr/g) values were 22.26, 864.43 and 58.72 for the oral 20 mg/kg, the oral 200 mg/kg, and the iv 20 mg/kg treatments, respectively. This disproportionate increase in the AUC value for the 200 mg/kg treatment in comparison to that of the 20 mg/kg treatment (38.8 times greater) was attributed to a saturation of the excretion pathway at the higher dosing level. The test material was largely recovered in the urine unmetabolized. **Study supplemental** (protocols used in the study were non-guideline) (Moore, 12/18/03)